A DISSERTATION FOR THE DEGREE OF MASTER

Determination of Tricuspid Regurgitation Velocity to Pulmonary Artery Flow Velocity Time Integral Ratio in Dogs with Pulmonary Hypertension

폐성고혈압 개에서 삼첨판 역류 속도와 폐동맥 혈류의 Velocity Time Integral 비율의 측정

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Abstract

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Pulmonary hypertension (PH) is a hemodynamic state in which the pressure of the pulmonary arterial vasculature is elevated. It causes variable range of clinical signs, such as cough, dyspnea, syncope and right-sided congestive heart failure (RCHF). The importance in veterinary clinics is associated with myxomatous mitral valve disease (MMVD), because of negative prognostic influence of PH. Right-heart catheterization is known to be a gold standard technique for diagnosing PH, however, alternative echocardiography is widely used for the clinical diagnosis because of its availability and non-invasiveness. There are many echocardiographic indices for evaluation of PH such as tricuspid regurgitation pressure gradient (TRPG), flow profile of right ventricular outflow tract, a ratio between main pulmonary artery: aorta ratio (MPA:Ao) and right pulmonary artery distensibility index (RPAD index).

This study was to determine the diagnostic value of systolic tricuspid regurgitation velocity to pulmonary artery flow velocity time integral ratio (TRV/VTI_{PA}), as a novel index in veterinary medicine, to predict the Doppler estimates of dogs with TRPG compared with other cardiac indices of PH. Furthermore, a cutoff value was investigated to evaluate patients with potentially poor outcome.

144 dogs were recruited with clear systolic tricuspid regurgitation on Doppler echocardiography. The dogs were allocated into four groups based on the echocardiography estimated TRPG. The groups were: (1) the normal group, dogs with a TRPG less than 36 mmHg, (2) mild PH, dogs with a

TRPG from 36 to 50 mmHg, (3) moderate PH, dogs with a TRPG from 50 to 75 mmHg and (4) severe PH, dogs with a TRPG over 75 mmHg. The correlation between the TRPG and cardiac indices was investigated. To define patients with poor outcome, dogs showed evidence of right sided congestive heart failure (RCHF) were included. Furthermore, the dogs in this group were compared with those without RCHF with TRPG more than 36 mmHg, in whom at least mild PH was suggested to be present.

A TRV/VTI_{PA} value increased significantly as the severity of PH increased ($P < 0.001$) and had correlation coefficient that was analogous to those of other conventional cardiac indices. A TRV/VTI_{PA} value greater 1.65 provided the best-balanced sensitivity (84%) and specificity (80%) in determining patients with poor prognosis.

The TRV/VTI_{PA}, which is readily obtained using routine echocardiography, could provide a non-invasive novel and supplementary index for evaluating dogs with PH, which could provide clinically good prognostic criteria, particularly for those with advanced PH.

Keywords: pulmonary hypertension, velocity time integral, echocardiography, dog

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Abbreviations

Ao	aorta
AT	acceleration time
BSA	body surface area
CO	cardiac output
ET	ejection time
HF	heart failure
ICC	intraclass correlation coefficient
MMVD	myxomatous mitral valve disease
MPA	main pulmonary artery
PAP	pulmonary arterial pressure
PCa	pulmonary arterial compliance
PH	pulmonary hypertension
PVR	pulmonary vascular resistance
RCHF	right-sided congestive heart failure
ROC	receiver operating characteristic curve
RPAD index	right pulmonary artery distensibility index
TRPG	tricuspid regurgitation pressure gradient
TRV	systolic tricuspid regurgitation velocity
VTI	velocity time integral

VTI$_{PA}$ pulmonary artery flow velocity time integral

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Introduction

Pulmonary hypertension (PH) is a hemodynamic state in which the pressure of the pulmonary arterial vasculature is elevated (Johnson *et al.*, 1999; Kellihan *et al.*, 2012; Stepien, 2009). PH is not a specific disease, but it is a complex syndrome that is caused by a wide range of primary cardiopulmonary and systemic etiologies (Johnson *et al.*, 1999; Stepien, 2009). It causes variable clinical signs, such as syncope, cough, dyspnea, exercise intolerance and right-sided congestive heart failure (RCHF) (Johnson *et al.*, 1999; Kellihan *et al.*, 2012; Stepien, 2009). In dogs with myxomatous mitral valve disease (MMVD), PH is especially associated with a poorer prognosis (Borgarelli *et al.*, 2015). Because of debilitating clinical symptoms and the negative prognostic influence of PH, a prompt and accurate diagnosis is required (Kellihan *et al.*, 2012). Right-heart catheterization is an accepted gold standard technique for diagnosing PH (Brecker *et al.*, 1994; Currie *et al.*, 1985). Pulmonary arterial pressure (PAP), pulmonary capillary wedge pressure, and cardiac output (CO) can be measured with right-heart catheterization to determine hemodynamic information regarding the presence and degree of PH (Ghio *et al.*, 2015). However, right-heart catheterization has less clinical value in veterinary medicine because of its invasiveness, cost, and the need for sedation or anesthesia, which can influence CO and measured pressures (Rhinehart, 2016). Alternatively, Doppler echocardiographic measurement is widely used for the clinical diagnosis of PH in dogs because of its availability and non-invasiveness (Johnson *et al.*, 1999; Kellihan *et al.*, 2010).

Indirect echocardiographic indices for PH, including the tricuspid regurgitation pressure gradient (TRPG), acceleration time of pulmonary artery flow (AT), AT: ejection time (ET), main pulmonary artery: aorta ratio (MPA:Ao), right pulmonary artery distensibility index (RPAD index), and other indices of right ventricular function (such as the systolic tricuspid annular plane systolic excursion, fractional area change, and myocardial performance index), have been proposed. While some studies showed that there was a very good correlation between these indices and catheterization derived parameters, others implied that these indices had clinical, technical and alignmental limitations (Kellihan *et al.*, 2010; Schober *et al.*, 2006; Serres *et al.,* 2007; Visser *et al.*, 2016).

PH is associated with pulmonary vascular resistance (PVR) (Koestenberger *et al.*, 2016; Kouzu *et al.*, 2009; Pande *et al.*, 2014) and pulmonary arterial compliance (PCa)(Ghio *et al.*, 2015; Troutman *et al.*, 2016; Bhattacharya *et al.*, 2017). PVR is calculated invasively as the transpulmonary pressure gradient divided by CO (Ghio *et al.*, 2015; Kouzu *et al.*, 2009). PCa is capable of supporting pulmonary pressure and is determined with the volume of single cardiac stroke. In human medicine, PCa, either alone or combined with PVR, gives clinicians a good stratification of the prognosis of PH or heart failure (HF) (Ghio *et al.*, 2015).

The pulmonary artery flow velocity time integral (VTI_{PA}) correlates well with PVR in human studies (Koestenberger *et al.*, 2016; Kouzu *et al.*, 2009; Pande *et al.*, 2014). In addition, the systolic tricuspid regurgitation velocity (TRV)/VTI_{PA} had a better correlation coefficient with PVR compared with that of VTI_{PA} alone (Kouzu *et al.*, 2009). More recently, VTI_{PA} was found to be strongly correlated with PCa and there was significant difference between PH and HF patients highlighting the need to further investigate the prognostic value and effect of therapy (Troutman *et al.*, 2016; Bhattacharya *et al.,* 2017). However, the reliability of echocardiographic VTI_{PA} measurements and the association between PVR and PCa have not been evaluated in dogs. Furthermore, the potential diagnostic value of VTI_{PA} in veterinary medicine is unknown.

Given that PVR and PCa correlated well with the TRV/VTI_{PA}

in human medicine studies, I assumed that the TRV/VTI_{PA} could be used as a novel index in dogs with PH and HF. It is hypothesized that the TRV/VTI_{PA} may predict the Doppler estimates of PAP and discriminate between the early and advanced stages of PH in those with RCHF. Therefore, I determined the diagnostic value of TRV/VTI_{PA} to predict the Doppler estimates of dogs with TRPG compared with other cardiac indices of PH. Furthermore, a cutoff value was investigated to select patients with a potentially poor outcome.

Materials and Methods

1. Animals

This retrospective study included 144 dogs that had clear TRV on Doppler echocardiography between August 2012 and August 2017. The dogs were divided into four groups based on the echocardiography estimated TRPG that was derived from the TRV. A simplified Bernoulli equation was used: $TRPG = 4 \times (TRV)^2$. The groups were: (1) the normal group; dogs with a TRPG less than 36 mmHg, (2) the mild PH group; dogs with a TRPG from 36 to 50 mmHg, (3) the moderate PH group; dogs with a TRPG from 50 to 75 mmHg and (4) the severe PH group; dogs with a TRPG greater than 75 mmHg. Exclusion criteria included right ventricular outflow tract obstruction, tricuspid valve dysplasia, ventricular septal defect, and history of taking sildenafil and other vasodilator such as amlodipine, hydralazine and nitroprusside. None of dogs showed evidence of dehydration and those undergoing fluid therapy were excluded from this study because of the possibility that fluid therapy would result in hemodynamic alterations. In the poor prognosis group, I included dogs that showed any signs of RCHF, such as ascites, pleural effusion, and hepatic congestion. Furthermore, the dogs in this group were compared with those without RCHF with a TRPG more than 36 mmHg, in whom at least mild PH was suggested to be present.

2. Echocardiographic measurements

Doppler echocardiography studies were performed with a machine (Aloka ProSound α7®; Hitachi Aloka Medical Ltd., Japan) using a 3−8 MHz phased array sector transducer (Hitachi Aloka Medical Ltd., Japan). The dogs were examined after manually restraining them in the right and left lateral recumbent position. The flow profile of the pulmonary artery with pulse−wave Doppler in the parasternal short axis view, and care was taken to optimize visualization of the MPA. The TRV was obtained with continuous−wave Doppler in the left apical, left long or short axis view. Care was taken to align the sample volume and axis of the blood stream correctly to obtain the highest and clearest Doppler velocity. Multiple cardiac cycles were recorded for each index. All data were stored on a separate workstation (Infinitt cardiology PACS; Infinitt Healthcare., Korea) to allow for off−line analysis. The following variables were measured: TRV(m/s), VTI_{PA} (cm), RPAD index (%), AT (ms), AT:ET and MPA:Ao.

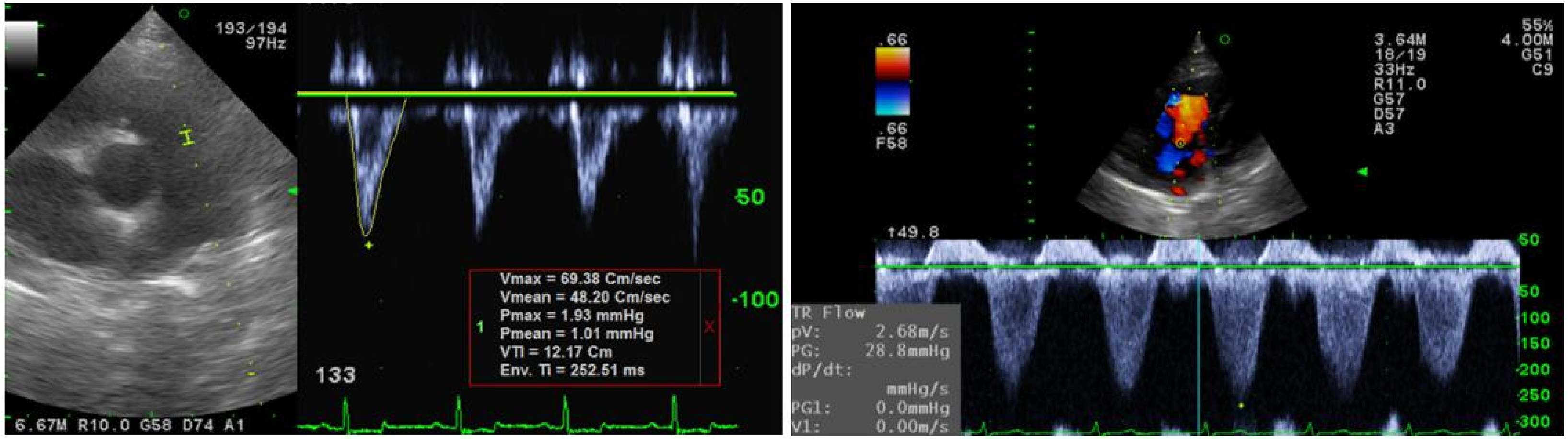

Figure 1. Images of VTI_{PA} (left) and TRV (right) in a dog with PH (VTI_{PA}: 12.17 cm, peak systolic TRV: 2.68 m/s).

VTI_{PA}, pulmonary artery flow velocity time integral; TRV, tricuspid regurgitation velocity; PH, pulmonary hypertension

3. Classification of PH

PH may be classified into a few categories, including pulmonary arterial hypertension, pulmonary venous hypertension, hypoxic PH, PH secondary to respiratory disease, PH secondary to thromboembolic disease, and PH secondary to miscellaneous etiologies. When all studies were combined, the causes of PH were classified briefly into pre- and postcapillary PH, or were based on the disease process that caused PH.

4. Statistical analysis

All echocardiographic measurements and calculations were performed by the same individual (SJK). An additional observer (DYO) assessed the reliability of the interobserver measurement. The value of the intraclass correlation coefficient (ICC) was interpreted as follows: over 0.75 was excellent, from 0.40 to 0.75 was fair to good, and less than 0.40 was poor (Fleiss, 1999).

All data were analyzed using statistical analysis software (SPSS, version 23, IBM corp., USA). Data are described as the mean and standard deviation. A P value of < 0.05 was considered statistically significant.

Normality was achieved with the Shapiro-Wilk test. Analysis of variance was used to evaluate difference among groups; subsequently a post hoc test was performed with Bonferroni's or Dunnett's test. The Kruskal Wallis test was used if the data did not show normality. The Jonckheere-Terpstra test was used to identify trends among groups. To predict the TRPG, using the cardiac indices, Pearson's correlation and a simple linear regression analysis were used. The Mann-Whitney's test was performed to identify whether the indices could predict poor prognosis. A receiver operating characteristic

(ROC) curve was used to suggest a cutoff value, sensitivity, and specificity.

Results

1. Clinical and echocardiographic data

The study population consisted of 144 dogs that were, allocated into four groups. There were no significant differences in body weight, body surface area (BSA), and age among the dogs in the four groups. There were 41 Maltese, 35 Shih Tzu, 14 Miniature Schnauzers, 11 Pekingese, 10 Cocker Spaniels, 8 mixed breeds, 7 Miniature Poodles, 6 Yorkshire Terriers, 3 Pomeranian, 2 Jindo, 2 Chihuahuas, 1 Dachshund, 1 French bulldog, 1 Miniature Pinscher, 1 Pug and 1 Cavalier King Charles Spaniel. Dogs in the severe PH group had a higher heart rate than did those in the normal and mild PH groups. A significantly higher number of dogs in the severe PH group had RCHF ($P < 0.05$) than did those in other groups.

All VTI measurements were adjusted by BSA. The echocardiographic data of the groups are presented in Table 1.

In the Jonckheere−Terpstra test, TRV/VTI_{PA} and MPA:Ao were increased and the VTI_{PA}, RPAD index, AT, and AT:ET were decreased as the severity of PH increased ($P < 0.001$).

Postcapillary PH that was caused by MMVD was the most common cause of PH in all groups. As the degree of PH worsened, the number of precapillary causes increased. Precapillary PH was mostly induced by heartworm and pulmonary disease, as well as suspected pulmonary thromboembolism.

Table 1. The clinical and echocardiographic characteristics of the dogs in this study (n = 144).

Data	Normal (n=41)	Mild PH (n=39)	Moderate PH (n=32)	Severe PH (n=32)
Body weight (kg)	5.2 ± 2.7	6.5 ± 3.7	5.0 ± 2.7	4.9 ± 1.9
BSA (m^2)	0.294 ± 0.093	0.337 ± 0.120	0.284 ± 0.103	0.283 ± 0.075
Heart rate (bpm)	128 ± 30	124 ± 26	142 ± 32	153 ± 32[a, b]
Age (years)	12.1 ± 2.1	12.4 ± 2.4	12.7 ± 3.1	11.4 ± 2.8
TRPG (mmHg)	29.8 ± 4.0	41.2 ± 3.6[a]	62.3 ± 7.2[a, b]	94.3 ± 22.3[a, b, c]
VTI_{PA} /BSA	45.4 ± 13.5	41.1 ± 12.2	37.4 ± 11.5[a]	32.2 ± 11.6[a, b]
(TRV/VTI_{PA})/BSA	0.86 ± 0.35	0.88 ± 0.39	1.66 ± 1.06[a, b]	2.32 ± 1.08[a, b, c]
RPAD index (%)	32.6 ± 7.3	26.7 ± 6.1[a]	22.2 ± 7.6[a, b]	15.0 ± 6.5[a, b, c]
AT	67.6 ± 18.3	66.9 ± 14.1	53.3 ± 13.0[a, b]	49.2 ± 13.4[a, b]
AT:ET	0.39 ± 0.10	0.38 ± 0.07	0.32 ± 0.05[a, b]	0.32 ± 0.08[a, b]
MPA:Ao	1.10 ± 0.10	1.09 ± 0.11	1.18 ± 0.14	1.27 ± 0.19[a, b, c]
RCHF (number)	1	1	5	14[a, b]

Data represented as mean ± standard deviation. PH, pulmonary hypertension; BSA, body surface area; TRPG, peak tricuspid regurgitation systolic pressure gradient; VTI_{PA}, pulmonary artery flow velocity time integral; TRV, systolic tricuspid regurgitation velocity; RPAD, right pulmonary artery distensibility; AT, acceleration time; ET, ejection time; MPA, main pulmonary artery; Ao, aorta; RCHF, right-sided congestive heart failure

[a] $P < 0.05$ when compared with the normal group. [b] $P < 0.05$ when compared with the mild PH group. [c] $P < 0.05$ when compared with the moderate PH group.

2. The correlation between echocardiographic measurements and TRPG

The TRV/VTI_{PA} had correlation coefficient (R = 0.48) that was analogous to that of other conventional cardiac indices for predicting TRPG. This parameter had lower correlation coefficient than did the RPAD index, but this parameter's correlation coefficient was higher than AT, AT:ET, and MPA:Ao.

To calculate the TRPG non−invasively, a simplified equation, which was derived from TRV/VTI_{PA} and VTI_{PA} was:

$$TRPG = (18.895 \times TRV/VTI_{PA}) + 28.512$$

$$TRPG = (-0.764 \times VTI_{PA}) + 84.569$$

Table 2. Results of the Pearson's correlation and simple linear regression analysis of the echocardiographic indices and TRPG.

Variable	R	R^2	P
VTI_{PA}/BSA	−0.37	0.14	< 0.001
(TRV/VTI_{PA})/BSA	0.48	0.23	< 0.001
RPAD index	−0.68	0.47	< 0.001
AT	−0.47	0.22	< 0.001
AT:ET	−0.39	0.15	< 0.001
MPA:Ao	0.32	0.10	< 0.001

R, correlation coefficient; R^2, determination coefficient

3. ROC curve to identify patients with poor prognosis

As PH progressed, mechanical consequences are marked increase in right ventricular afterload, resulting in RCHF. HF is known to be highly lethal, which was consistent with the results of this study. In this study, dogs in the RCHF group had a significantly low median survival time (106 days) and high mortality (86.7%) compared with dogs without RCHF in the PH group (173 days and 45.2%, respectively).

In dogs in the RCHF group, the TRV/VTI_{PA} was significantly increased (P < 0.001) and the RPAD index (P = 0.033) was significantly decreased compared with those in dogs in the PH group. Using the ROC analysis, I found that a TRV/VTI_{PA} cutoff value of 1.65 provided the best-balanced sensitivity (84%) and specificity (80%) to determine patients with poor prognosis (area under the curve: 0.863). However, the RPAD index did not have clinical value to predict the patient's prognosis (area under the curve: 0.224).

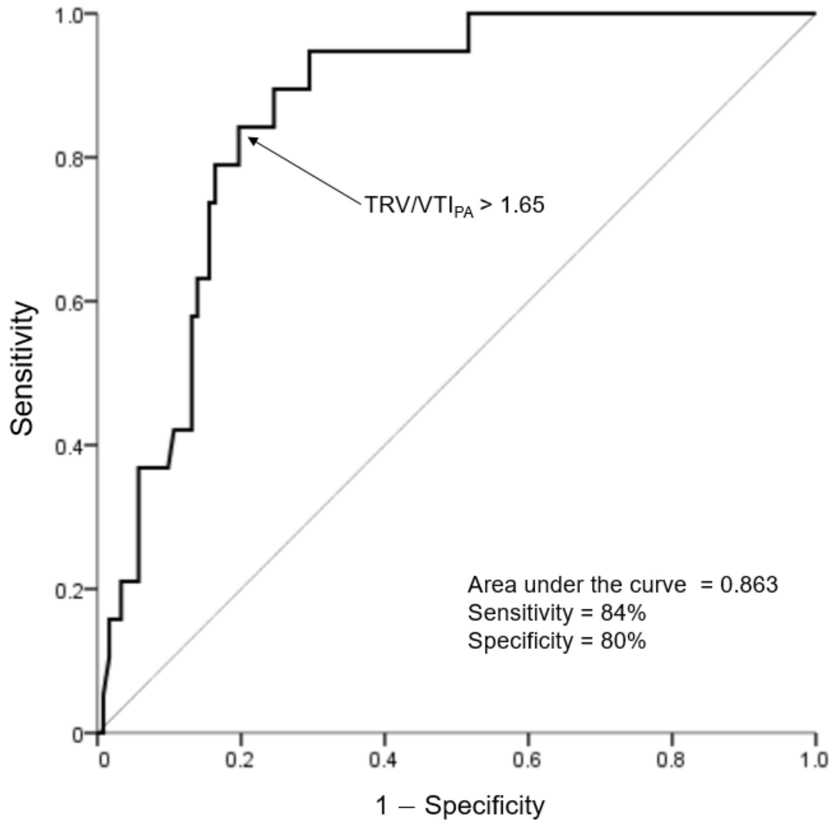

Figure 2. The ROC curve. A TRV/VTI$_{PA}$ value of 1.65 provided a sensitivity of 84% and specificity of 80% (area under the curve: 0.863, 95% confidence interval: 0.794 to 0.932) to identify patients with a poor prognosis.

ROC, receiver operating characteristic curve; TRV/VTI$_{PA,}$ tricuspid regurgitation velocity/pulmonary artery flow velocity time integral

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4. Intraobserver and interobserver reliabilities

In the intra- and interobserver agreement analysis, the ICCs of the VTI_{PA} were excellent (ICCs > 0.9, $P < 0.001$).

Discussion

In this study, I observed that TRV/VTI_{PA} increased with the severity of PH, and there was an analogous, linear correlation between the TRPG and Doppler−estimated TRV/VTI_{PA} or VTI_{PA} compared with other cardiac indices of PH. Additionally, a TRV/VTI_{PA} over 1.65, with a sensitivity of 84% and specificity of 80%, suggested that dogs with PH had poor prognosis.

Various echocardiographic indices have been used routinely to determine PH; however, such indices have some pitfalls. Several studies reported that the heart rate has a significant effect on the ventricular systolic time interval (AT and AT:ET) in dogs (Atkins *et al.*, 1992; Pipers *et al.*, 1978). However, another study indicated that age and heart rate have only negligible effects on these indices (Schober *et al.*, 2006). Echocardiographic heart remodeling such as septal flattening or increased MPA:Ao may be observed in dogs with moderate to severe PH, but these changes are insensitive in dogs with in mild PH (Kellihan *et al.*, 2010). TRPG, which is used routinely to estimate PAP, has limitations, especially when evaluating patients who receive vasodilators. Sildenafil is frequently used to treat PH in dogs to decrease PVR; the consequences include increasing CO, whereas the PAP does not change significantly. Therefore, assessing the TRPG alone could underestimate the hemodynamic changes of vasodilators unless the patient remain untreated (Kouzu *et al.*, 2009).

An accurate evaluation of pulmonary circulation requires an understanding of both its static and dynamic components. PVR and PCa are hemodynamic concepts that are frequently used in clinical practice in humans. PVR is most frequently used to measure right ventricular afterload, but it has limitation as a static component. Reduced PCa is known to be a powerful marker of poor prognosis in patients with idiopathic pulmonary arterial hypertension and those with HF. Moreover, studies suggest that PH could be better diagnosed in the early stage through alteration of PCa, rather than increase in PVR (Ghio *et al.*, 2015). However, measuring these hemodynamic components *in vivo*, especially in veterinary medicine, is difficult due to its invasiveness and the patient's need for additional sedatives or anesthetics. As alternatives, VTI is available by means of non-invasive parameter.

Many studies have demonstrated that there is a correlation between the TRV/VTI_{PA} and PVR in patients with PH (Kouzu *et al.*, 2009; Koestenberger *et al.*, 2016; Pande *et al.*, 2014; Abbas *et al.*, 2013) and suggested normal value by age in pediatrics

(Koestenberger *et al.,* 2015). Moreover, evaluating the VTI_{PA} in HF patients has been shown to be feasible in some studies (Troutman *et al.*, 2016; Bhattacharya *et al.*, 2017). VTI is closely related to CO; the consequences of low CO are cardiogenic shock, multi-organ dysfunction, and even death (Abraham *et al.*, 2005). Studies have shown that a low VTI in either the right or left ventricular outflow tract correlates with adverse clinical outcomes (Kouzu *et al.*, 2009; Tan *et al.*, 2017). A recent study found that rapid ultrasound in shock (the RUSH examination) using VTI is an emerging protocol to identify the source of shock or hypotension and predict the patient's response to treatment in the emergency department (Blanco *et al.*, 2015).

The precapillary cause of PH, in which the PAP is markedly elevated, induces considerable echocardiographic alterations such as septal flattening and paradoxical septal motion (Serres *et al.*, 2007). Although, the progression of postcapillary PH is relatively slow, a hypertensive left ventricle adversely affects the compliance and filling of the contralateral right ventricle, resulting in a cycle of vicious impact on function in the two ventricles (Bronicki *et al.*, 2010). In veterinary clinics, MMVD that is associated with moderate to severe PH is also associated with shorter survival times (Borgarelli *et al.*, 2015).

Therefore, estimating the TRV/VTI_{PA} may be useful to assess disease over time and predict the prognosis of patients with acute or chronic PH progression.

Many studies suggested using the equation of TRV/VTI_{PA} to estimate the PVR and determine the TRV/VTI_{PA} cutoff value for screening patients with a high PVR (Koestenberger *et al.*, 2016; Pande *et al.*, 2014; Pipers *et al.*, 1978; Schober *et al.*, 2006). However, its reliability differs according to various inclusion criteria (Atkins *et al.,* 1992; Tan *et al.*, 2017). For example, in one study, echocardiography was shown to be useful to screen patients with PH and PVR greater than 2 wood units using TRV/VTI_{PA} value of 0.14 as the cutoff. However, the authors of that study concluded that this cutoff value was disappointing for the accurate assessment of high PVR (Roule *et al.*, 2010). Alternatively, another study suggested a linear regression equation that was applicable to patients who had severe PH with a PVR greater than 6 wood units (Ajami *et al.*, 2011). Because the pulmonary pressure in dogs included in this study ranged broadly and the hemodynamic values could not be measured directly, the linear regression equation in this study needs further validation. Because there is an absence of studies about a normal VTI value that is based on age, BSA, heart rate, and various cardiopulmonary diseases, further studies are needed to evaluate healthy and ill dogs.

A study on humans used the hemodynamic variables that are recommended by international guidelines to define those with a poor prognosis and select candidates for lung transplantation (Kouzu *et al.*, 2009). In this study, group of poor prognosis were confined to dogs with RCHF. Unlike in human medicine, in veterinary medicine, identifying RCHF depends entirely on the evidence that is seen on radiography or ultrasonography, such as ascites, pleural effusion, hepatic congestion, and pericardial effusion. Therefore, the cutoff value that was suggested in this study could be overestimated or inaccuracy.

VTI_{PA} was first introduced as an index that is measured with Doppler echocardiography in a study in veterinary medicine about independent factors such as body position, sedation, and exercise that influence echocardiographic indices (Rhinehart, 2016). To author's knowledge, the diagnostic significance of VTI_{PA} has not been evaluated in veterinary medicine so far. According to the results of this study, TRV/VTI_{PA} increased as PH worsened. Therefore, it could be a non-invasive, novel and supplementary index to evaluate the degree of PH. Particularly, it allows for good clinical stratification of the prognosis of advanced PH.

This study has some limitation. Client−owned dogs were included, and the degree and presence of PH were determined with the TRPG, although VTI is closely related to PVR or PCa. For reasons mentioned above, non−invasively calculated PAP that is derived from the peak TRV was used in this study. This method is less accurate than invasively determined PAP (Brecker *et al.*, 1994; Uehara, 1993). I neglected to study right arterial pressure to estimate the Doppler derived PAP. The accuracy of invasive, systolic PAP was minimally improved when adding right arterial pressure to the TRPG (Soydan *et al.*, 2015). Another study noted that calculating the right arterial pressure may result in overestimation of the severity of PH in humans (Fisher *et al.*, 2009). Many studies that evaluated the relationship between Doppler echocardiography−derived PAP and various cardiac indices showed similar results, although slightly different methods were used in each study to estimate PAP.

This study is the first in which the importance of VTI_{PA} was evaluated in dogs with PH. In clinical practice, VTI_{PA} could provide additional information on individual hemodynamics as an alternative to PVR and PCa. Moreover, the TRV/VTI_{PA} cutoff value can be judged roughly as acceptable or abnormally impaired in patients with PH. As a non−invasive parameter to determine the degree of PH, I propose including TRV/VTI_{PA} in echocardiographic protocols for patients with PH.

References

Abbas AE, Franey LM, Marwick T, Maeder MT, Kaye DM, Vlahos AP, Serra W, Al-Azizi K, Schiller NB, Lester SJ. Noninvasive assessment of pulmonary vascular resistance by Doppler echocardiography. J Am Soc Echocardiogr 2013;26:1170-1177.

Abraham WT, Adams KF, Fonarow GC, Costanzo MR, Berkowitz RL, LeJemtel TH, Cheng ML, Wynne J. In-hospital mortality in patients with acute decompensated heart failure requiring intravenous vasoactive medications: an analysis from the acute decompensated heart failure National Registry. J Am Coll Cardiol 2005;46(1):57.

Ajami GH, Cheriki S, Amoozgar H, Borzouee M, Soltani M. Accuracy of Doppler-derived estimation of pulmonary vascular resistance in congenital heart disease: An index of operability. Pediatr Cardiol 2011;32:1168-1174.

Atkins CE, Snyder PS. Systolic time intervals and their derivatives for evaluation of cardiac function. J Vet Intern Med 1992;6:55–63.

Bhattacharya PT, Fox A, Tanna MS, Troutman GS, Mao FJ, Menachem JN, Birati EY, Forfia P, Vaidya A, Mazurek JA. Right ventricular outflow tract−velocity time integral and pulmonary artery systolic pressure ratio: A novel non−invasive marker of pulmonary arterial compliance in pulmonary arterial hypertension vs. pulmonary hypertension in heart failure with preserved ejection fraction. Am J Respir Crit Care Med. 2017;195:A6176.

Blanco P, Aguiar FM, Blaivas M. Rapid ultrasound in shock (RUSH) velocity−time integral: A proposal to expand the RUSH protocol. J Ultrasound Med. 2015;34(9):1691−1700.

Borgarelli M, Abbott J, Braz−Ruivo L, Chiavegato D, Crosara S, Lamb K, Ljungvall I, Poggi M, Santilli RA, Haggstrom J. Prevalence and prognostic importance of pulmonary hypertension in dogs with myxomatous mitral valve disease. J Vet Intern Med 2015;29:569−574.

Brecker SJ, Gibbs JS, Fox KM, Yacoub MH, Gibson DG. Comparison of Doppler derived haemodynamic variables and simultaneous high fildelity pressure measurements in severe pulmonary hypertension. Br Heart J 1994;72:384-389.

Bronicki RA, Baden HP. Pathophysiology of right ventricular failure in pulmonary hypertension, Pediatr Crit Care Med 2010;2:S15-S22.

Currie PJ, Seward JB, Chan KL, Fyfe DA, Hagler DJ, Mair DD, Reeder GS, Nishimura RA, Tajik AJ. Continuous wave Doppler determination of right ventricular pressure: a simultaneous Doppler-catheterization study in 127 patients. J Am Coll Cardiol 1985;6:750-756.

Fisher MR, Forfia PR, Chamera E, Housten-Harris T, Champion HC, Girgis RE, Corretti MC, Hassoun PM. Accuracy of Doppler echocardiography in the hemodynamic assessment of pulmonary hypertension. Am J Respir Crit Care Med 2009;179:615-621.

Fleiss JL. Design and analysis of clinical experiments. New York: Wiley; 1999:23–27.

Ghio S, Schirinzi S, Pica S. Pulmonary arterial compliance: How and why should we measure it?. Glob Cardiol Sci Pract 2015;4:58.

Ihlen H, Amlie JP, Dale J, Forfang K, Nitter-Hauge S, Otterstad JE, Simonsen S, Myhre E. Determination of cardiac output by Doppler echocardiography. Br Heart J 1984;51:54–60.

Johnson L, Boon J, Orton EC. Clinical characteristics of 53 dogs with Doppler-derived evidence of pulmonary hypertension: 1992–1996. J Vet Intern Med 1999;13:440–447.

Kellihan HB, Stepien RL. Pulmonary hypertension in dogs: diagnosis and therapy. Vet Clin North Am Small Anim Pract 2010;40:623–641.

Kellihan HB, Stepien RL. Pulmonary hypertension in canine degenerative mitral valve disease. J Vet Cardiol 2012;14:149-164.

Koestenberger M, Nage B, Ravekes W, Avian A, Burmas A, Grangl G, Cvirn G, Gamillscheg A. Right ventricular outflow tract velocity time integral determination in 570 healthy children and in 52 pediatric atrial septal defect patients. Pediatr Cardiol 2015; 36:1129-1134.

Koestenberger M, Avian A, Grangl G, Burmas A, Kurath-Koller S, Hansmann G. Right ventricular outflow tract velocity (RVOT VTI) and tricuspid regurgitation velocity/RVOT VTI ratio in pediatric pulmonary hypertension. Int J Cardiol 2016;212:274-276.

Kouzu H, Nakatani S, Kyotani S, Kanzaki H, Nakanishi N, Kitakaze M. Noninvasive estimation of pulmonary vascular resistance by Doppler echocardiography in patients with pulmonary arterial hypertension. Am J Cardiol 2009;103:872-876.

Pande A, Sarkar A, Ahmed I, Naveen Chandra G, Patil SK, Kundu CK, Arora R, Samanta A. Non-invasive estimation of pulmonary vascular resistance in patients of pulmonary hypertension in congenital heart disease with unobstructed pulmonary flow. Ann Pediatr Cardiol 2014;7:92-97.

Pipers FS, Andrysco RM, Hamlin RL. A totally non-invasive method for obtaining systolic time intervals in the dog. Am J Vet Res 1978;39:1822-1827.

Rhinehart JD. Clinical Evaluation of Echocardiographic Variability in Estimating Pulmonary Artery Pressure and Pulmonary Vascular Resistance in Dogs [dissertation]. Ohio (OH): The Ohio State University; 2016.

Roule V, Labombarda F, Pellissier A, Sabatier R, Lognone T, Gomes S, Bergot E, Milliez P, Gollier G, Saloux E. Echocardiographic assessment of pulmonary vascular resistance in pulmonary arterial hypertension. Cardiovasc Ultrasound 2010;8:21.

Schober KE, Baade H. Doppler echocardiographic prediction of pulmonary hypertension in West Highland white terriers with chronic pulmonary disease. J Vet Intern Med 2006;20:912–920.

Serres F, Chetboul V, Gouni V, Tissier R, Sampedrano CC, Pouchelon JL. Diagnostic value of echo-Doppler and tissue Doppler imaging in dogs with pulmonary arterial hypertension. J Vet Intern Med 2007;21:1280–1289.

Soydan LC, Kellihan HB, Bates ML, Stepien RL, Consigny DW, Bellofiore A, Francois CJ, Chesler NC. Accuracy of Doppler echocardiographic estimates of pulmonary artery pressures in a canine model of pulmonary hypertension. J Vet Cardiol 2015;17:13–24.

Stepien RL. Pulmonary arterial hypertension secondary to chronic left-sided cardiac dysfunction in dogs. J Small Anim Pract 2009;50:34–43.

Tan C, Rubenson D, Srivastava A, Mohan R, Smith MR, Billick K, Bardarian S, Thomas Heywood J. Left ventricular outflow tract velocity time integral outperforms ejection fraction and Doppler derived cardiac output for predicting outcomes in a select advanced heart failure cohort. Cardiovasc Ultrasound 2017;15:18.

Troutman GS, Bhattacharya PT, Grandin EW, Menachem JN, Birati EY, Golbus JR, Forfia PR, Vaidya A, Mazurek JA. Right ventricular outflow tract velocity time integral to pulmonary artery systolic pressure ratio: A new non-invasive metric of pulmonary arterial compliance. J Card Fail 2016;22:S47-48.

Uehara Y. An attempt to estimate the pulmonary artery pressure in dogs by means of pulsed Doppler echocardiography. J Vet Med Sci 1993;55:307–312.

Visser LC, Im MK, Johnson LR, Stern JA. Diagnostic value of right pulmonary artery distensibility index in dogs with pulmonary hypertension: comparison with Doppler echocardiographic estimates of pulmonary artery pressure. J Vet Intern Med 2016;2:543-552.

국문초록

폐성고혈압 개에서 삼첨판 역류 속도와 폐동맥 혈류의 Velocity Time Integral 비율의 측정

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폐성고혈압은 폐동맥의 압력이 증가된 혈류역학적 상태이다. 이는 기침, 호흡곤란, 기절, 심부전과 같은 다양한 임상 증상을 야기한다. 임상수의학에서 폐성고혈압은 이첨판폐쇄부전 환자에서 부정적인 예후 인자로 알려져 있다. Right heart catheterization은 폐성고혈압의 진단의 골드스다드로 알려져 있으나, 임상적 진단 시 심장 초음파는 접근이 쉽고 비침습적이기 때문에 대체 진단법으로 널리 쓰이고 있다. 심장초음파를 통한 폐성고혈압의 평가에는 삼첨판역류압력경도 (TRPG), 우심실유출로의 혈류 파형, 주폐

동맥과 대동맥의 비율, 우폐동맥 확장 인덱스 등의 지표들이 유효하다.

이번 연구는 수의학에 도입된 새로운 지표로서, 삼첨판역류속도와 폐동맥혈류의 velocity time integral의 비율 (TRV/VTI_{PA}) 이 TRPG의 예측에 어느 정도의 진단적 가치를 지니는지 알아보고자 하였다. 또한 불량한 예후를 보이는 폐성고혈압 환자 평가에 적용될 수 있는 판정기준치를 정립하고자 한다.

도플러 심장 초음파에서 명확한 삼첨판 역류 파형을 보이는 144마리의 개가 연구에 사용되었다. 환자는 TRPG에 따라 네 그룹 중 하나로 분류되었다. (1) 정상군, TRPG 36 mmHg 미만 시, (2) 경도의 폐성고혈압군, TRPG 36–50 mmHg 사이, (3) 중등도의 폐성고혈압군, TRPG 50–75 mmHg 사이, (4) 고도의 폐성고혈압군, TRPG 75 mmHg 초과. 측정된 심장초음파 지표와 TRPG와의 상관관계가 연구되었다. 예후 불량한 환자의 설정은 울혈성 우심부전의 근거를 보이는 개체로 정의되었다. 그리고 이들은 최소 경도의 폐성고혈압을 보이는 TRPG 36 mmHg 이상의 환자와 비교되었다.

TRV/VTI_{PA} 수치는 폐성고혈압이 심화될수록 ($P < 0.001$) 증가하였으며, 기존의 다른 초음파 지표와 유사한 상관계수를 보였다. 또한 예후 불량 환자의 판단에 있어서, 기준치 1.65 이상일 때 가장 훌륭한 민감도 (84%)와 특이도 (80%)를 보였다.

주요어: pulmonary hypertension, velocity time integral, echocardiography, dog

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